REMARKS

Claims 1-88 are pending in this application. Of these, Claims 43, 54, 67-69, and 77-88 are withdrawn from consideration. Claims 1-42, 44-53, 55-66, and 70-76 stand rejected. Claim 66 has been amended to correct a typographical error in dependency. Applicants respectfully request reconsideration and allowance of Claims 1-42, 44-53, 55-66, and 70-76.

Rejection of Claims Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,741,899 (Capon et al.). According to the Examiner, Capon et al. teaches (1) a chimeric protein comprising an intracellular or extracellular inducer-responsive clustering domain capable of binding an inducer (*e.g.*, FKBP) and a proliferation signaling domain that signals a host cell to divide (*e.g.*, G-CSFR, EPO-R, gp130 etc.); (2) a multivalent cell-permeant inducer drug with a molecular weight less than 5 kD; and (3) cells that can be induced to expand by transducing them *in vivo* or *in vitro* by an appropriate vector expressing such chimeric proteins for the treatment of human diseases such as cancer and autoimmune disease. Thus, the Examiner concludes that Capon et al. anticipates the claimed invention. Applicants respectfully disagree.

An anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). Capon et al. describes the construction of various chimeric proliferation receptors (CPRs) comprising an inducer-responsive clustering domain linked to a proliferation signaling domain (*see* Capon et al., EXAMPLES 1-9), and their expression in 293 cells (Capon et al., EXAMPLE 10) or human $CD8^+$ T lymphocytes (Capon et al., EXAMPLE 11). However, Capon et al. does not provide an enabling disclosure of (a) drug-induced proliferation of primary cells using these CPRs,

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(b) transduction of cells in a mammal with a recombinant DNA construct encoding a CPR, and (c) administration of the drug to the mammal, as described below.

Independent Claim 1, from which Claims 2-20 depend, recites a method for rendering a subpopulation of primary mammalian cells susceptible to drug-induced growth, proliferation, or differentiation, comprising transducing the cells with a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein exposure of the transduced cells to the drug induces growth, proliferation, or differentiation of the cells. Independent Claims 21, from which Claims 32-41 depend, and independent Claim 22 are directed to methods for expanding a subpopulation of primary cells by transducing the primary cells with a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain and treating or exposing the transduced cells to the drug. Independent Claim 44, from which Claims 45-53 depend, is directed to a genetically engineered primary mammalian cell containing a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein exposure of the genetically engineered primary cells to the drug induces growth, proliferation, or differentiation of the cells. Claim 55 is directed to an *ex vivo* culture of the cells of Claims 44-53. Independent Claim 56, from which Claims 57 and 58 depend, and Claim 59 are directed to a method for treating or preventing a hematopoietic disease or pathological condition in a mammal by introducing into the mammal the genetically engineered primary cells of Claim 46 or the transduced primary cells of Claim 24, respectively. Claims 60-62 are directed to methods for obtaining populations of hematopoietic cells containing a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein exposure of the transduced cells to the drug induces growth, proliferation, or differentiation of the cells. Independent Claim 63, from which Claim 64 depends, is directed to a method for treating a hematopoietic disease or pathological condition in

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a mammal by introducing into the mammals cells containing a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein exposure of the transduced cells to the drug induces growth, proliferation, or differentiation of the cells, and administering the drug to the mammal. Independent Claim 65, from which Claim 66 depends, is directed to a method for rendering a mammal susceptible to treatment for hematopoietic disease by providing the mammal with cells containing a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein exposure of the binding of the drug to the drug-binding domain induces proliferation of the cells. Independent Claim 70, from which Claims 71-76 depend, is directed to a method for administering hematopoietic stem cell therapy to a mammal by harvesting primary cells from a donor mammal, transducing them with a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain, wherein multimerization of the fusion protein induces growth, proliferation, or differentiation, introducing the transduced cells into a recipient mammal, and administering the drug to the recipient mammal. In sum, Claims 1-42, 44-53, 55-66, and 70-76 are directed to primary cells and methods of making and using these cells, wherein the cells express CPRs that render the cells sensitive to drug-induced growth, proliferation, or differentiation. Claims 19, 20, 39, and 40 additionally recite that the primary cells are transduced within the mammal with a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain. Claims 42, 57, 63, 64, 66, and 70-76 additionally recite that the drug is administered to the mammal.

Capon et al. does not provide an enabling disclosure of drug-induced proliferation of primary cells using CPRs. The only description of expression of CPRs in primary cells provided by Capon et al. is EXAMPLE 11. In EXAMPLE 11, human $CD8^+$ T lymphocytes were transfected with CPRs comprising the extracellular inducer-responsive clustering domain CD4

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linked to Janus kinase proliferation signaling domains. The transfected cells were shown to express the CPRs. However, expression of CPRs in transfected cells does not mean that these CPRs are functional. As acknowledged by Capon et al. "[o]nce one has established that the transformed host cell expresses the CPR of the present invention . . . , one may then determine whether the CPR is function in the host cell by providing the desired proliferation signal." (Capon et al., Column 18, lines 43-47). In EXAMPLE 11, the transfected cells are prophetically exposed to "OKT4A, anti-human Fc Mab, gp120, gp160-expressing cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Capon et al., Column 42, lines 62-64). However, there is no description of proliferation occurring after exposure to any of these inducers. Moreover, the only drug among this list of inducers, FK1012, would be ineffective to stimulate proliferation of these transfected cells because none of the CPRs used in this experiment comprised an FK1012-binding domain (such as FKBP).

Furthermore, applicants' publication describing the expression of a fusion protein comprising FKBP and mpl in primary cells, resulting in the proliferation of these cells in the presence of FK1012, notes that "[t]o our knowledge, these results provide the first example of cell proliferation that is dependent on a synthetic drug" (Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3076, Column 2). This is corroborated by a review of this paper in *Science*, stating that "these results create a novel on/off switch to control mitogenic signaling" (Sikorski & Peters (1997) *Science* 276(5320):1891).

Therefore, Capon et al. does not provide an enabling disclosure for drug-induced proliferation of primary cells using a fusion comprising at least one signaling domain and at least one drug-binding domain, as required by Claims 1-42, 44-53, 55-66, and 70-76, and these claims are neither anticipated nor obvious in view of this reference.

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Capon et al. also does not disclose or suggest transduction of cells within the mammal with a recombinant DNA construct encoding a CPR. As noted above, Claims 19, 20, 39, and 40 additionally recite that the primary cells are transduced within the mammal with a recombinant DNA construct encoding a fusion protein with a signaling domain and a drug-binding domain. For example, cells are transduced within the mammal by administering to the mammal a viral or other DNA vector containing the DNA construct encoding a CPR (see Specification, page 4, lines 13-33). In contrast, Capon et al. only describes transducing DNA constructs encoding a CPR into host cells *in vitro*. Specifically, in the only passage describing the introduction of the constructs into cells, Capon et al. state :

> The chimeric construct may be introduced the target cell in any convenient manner. Techniques include calcium phosphate or DEAE-dextran mediated DNA transfection, electroporation, protoplast fusion, liposome fusion, biolistics using DNA-coated particles, and infection, where the chimeric construct is introduced into an appropriate virus (eg retrovirus, adenovirus, adeno-associated virus, Herpes virus, Sindbis virus, papilloma virus), particularly a non-replicative form of the virus, or the like. In addition, direct injection of naked DNA or protein- or lipid-complexed DNA may also be used to introduce DNA into cells (Capon et al., Column 19, lines 17-27).

This passage conveys to one of skill in the art that the introduction of the constructs encoding the CPRs occurs in cells cultured outside the body. Capon et al. describes that the cells expressing the CPRs are subsequently introduced into the body:

> Other cell types that would be of particular interest for expansion after delivery of the CPRs of the subject invention are islets of Langerhans which may be grown and introduced into a host by capsules or other means, for the production of insulin. Retinal epithelial cells may also be expanded and injected or implanted into the subretinal space of the eye to treat visual disorders, such as macular degeneration. Immune cells, described in detail above, may be expanded ex vivo and injected into the bloodstream or elsewhere to treat immune deficiency. Myoblasts may be expanded with the present invention and injected at various sites to treat muscle wasting diseases such as Duchenne muscular dystrophy. Hepatocytes may be expanded for use in liver regeneration. Endothelial cells may also be expanded to repair blood vessels or to deliver proteins to the circulation. Nerve cells which ordinarily do not proliferate may be targets for expression by using the CPRs of present invention. In addition cells which will not

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> proliferate in vitro, and therefore cannot be manipulated or genetically engineered may be ideal recipients of the CPRs of the present invention (Capon et al., Column 21, lines 16-35).
>
> The recipient of genetically modified allogeneic cells can be immunosuppressed to prevent the rejection of the transplanted cells. In the case of immunocompromised patients, no pretransplant therapy may be required. Another alternative source of cells to be transplanted are so-called "universal donor" cells which have been genetically engineered so that they do not express antigens of the major histocompatibility complex or molecules which function in antigen presentation (Capon et al., Column 21, lines 55-63).

Thus, Capon et al. clearly only contemplates engineering cells *in vitro* to express CPRs, then introducing the engineered cells into a host. Moreover, in the two working examples in Capon et al. describing expression of CPRs in target cells, transfection or infection of cells *in vitro* is used to introduce the DNA constructs encoding CPRs (Capon et al., Examples 10 and 11). Therefore, Capon et al. does not disclose transduction of cells within the mammal with a recombinant DNA construct encoding a CPR, as required by Claims 19, 20, 39, and 40.

Capon et al. also does not disclose or suggest administration of the drug *in vivo*. As noted above, Claims 42, 57, 63, 64, 66, and 70-76 additionally recite that the drug is administered to the mammal. Although, Capon et al. describe the expansion of CPR-expressing cells in an animal in response to an inducer, the inducer used is not administered and is not a drug. Specifically, Capon et al. describe CPR-expressing cells that will proliferate within the animal in response to an inducer *that is already present within the animal*, such as antigens present on neoplastic cells, virus-infected cells, parasite-infected cells (see, e.g., Capon et al., Column 16, lines 7-44; Column 20, lines 14-67). As described above, the only description in Capon et al. of the administration of a drug to CPR-expressing cells is in EXAMPLE 11, in which transfected cells are prophetically exposed to "OKT4A, anti-human Fc Mab, gp120, gp160-expressing cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Capon et al., Column 42, lines 62-64). However, these transfected cells are exposed to the drug,

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FK1012, *in vitro*, not in an animal. In addition, the CPRs expressed by the cells did not contain an FK1012-binding domain. Thus, exposure of the cells to the drug would not lead to the proliferation of the CPR-expressing cells. Therefore, Capon et al. does not disclose or suggest administration of the drug *in vivo*, as required by Claims 42, 57, 63, 64, 66, and 70-76.

For the reasons set forth above, it is respectfully submitted that Capon et al. does not anticipate or render obvious applicants' Claims 1-42, 44-53, 55-66, and 70-76, and that the Examiner's rejection of claims under 35 U.S.C. § 102 should properly be withdrawn.

Information Disclosure Statement

The Examiner has noted that the Supplemental Information Disclosure Statement filed on August 30, 2002, had not been signed by the attorney of record. A signed Second Supplemental Information Disclosure Statement is submitted herewith. Applicants respectfully request consideration of the references in the Second Supplemental Information Disclosure Statement.

Conclusion

In view of the foregoing comments, Claims 1-42, 44-53, 55-66, and 70-76 are believed to be in condition for allowance. Reconsideration and favorable action is requested.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: 5/21/03 Carole Julyan

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VERSION WITH MARKINGS TO SHOW CHANGES MADE MAY 21, 2003

In the Claims:

66. (Amended) A method for treating a hematopoietic disease, comprising administrating to a patient that has been made susceptible to treatment for a hematopoietic disease by the method of Claim ~~63~~65 a drug that binds said drug binding domain.

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